REMARKS

Specification Amendments

The specification has been amended to correctly recite that the subject application is a continuation-in-part of U.S. Application 09/904,090 filed July 12, 2001. A Declaration for Patent Application was filed on May 10, 2002. In an abundance of caution, a Supplemental Declaration will be filed separately in the subject application.

The specification has been amended at various locations to recite the proper notation for the sequence identifiers. The specification has also been amended to recite nomenclature that is more commonly used in the art for SEQ ID NO: 4. That is, a molecule amidated with "-NH_2" at the C-terminus means that the -COOH group at the C-terminus is replaced with -$CONH_2$. No new matter has been added by this amendment to the specification.

New Claims 29-42

The subject matter of new Claims 29-41 is fully supported in the present application as filed January 16, 2002. Support can be found in the specification, for example, at page 2, lines 18-21; page 3, lines 6-25; page 5, line 3 to page 6, line 11; page 7, line 9 to page 10, line 4; page 10, line 14-15; and in originally filed Claims 7-8 and 25-26.

New Claims 29-41 recite the same peptide as in original Claims 7-8 and 25-26, i.e., amidated at the C-terminus with -NH_2. However, the nomenclature used to represent this peptide in new Claims 29-42 is more commonly used in the art. That is, a molecule amidated with "-NH_2" at the C-terminus means that the -COOH group at the C-terminus is replaced with -$CONH_2$. No new matter has been added by the new claims.

Substitute Sequence Listing

Transmitted concurrently herewith is a copy of a Substitute "Sequence Listing" in paper form (sheets 1/2 through 2/2) comprising SEQ ID NOs: 1-5 for the above-identified patent application as required by 37 C.F.R. §§ 1.825(a) and 1.821(c), and a copy of the Substitute "Sequence Listing" in computer readable form as required by 37 C.F.R. §§ 1.825(b) and 1.821(e).

Please replace the "Sequence Listing" filed on May 10, 2002 (sheets 1/2 through 2/2) with the attached Substitute "Sequence Listing".

The Substitute "Sequence Listing" includes SEQ ID NO: 5, which had been inadvertently omitted from the "Sequence Listing" filed on May 10, 2002. The Substitute "Sequence Listing" also recites nomenclature that is more commonly used in the art for SEQ ID NO: 4. That is, a molecule amidated with "-NH_2" at the C-terminus means that the -COOH group at the C-terminus is replaced with -$CONH_2$. No new matter has been added with the Substitute "Sequence Listing".

As required by 37 C.F.R. § 1.825(b), Applicant's Attorney hereby states that the contents of the Substitute "Sequence Listing" in paper form and in the computer readable form submitted herewith are the same and, as required by 37 C.F.R. § 1.825(a), also states that the submission includes no new matter.

Item 1: Information Disclosure Statement

An Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry and consideration of the IDS are respectfully requested.

Items 2 to 6: Rejection of Claims 1, 6, 9-19, 24, 27 and 28 Under 35 U.S.C. § 112, First Paragraph

Claims 1, 6, 9-19, 24, 27 and 28 have been rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the specification does not reasonably provide enablement for all angiogenic thrombin derivative peptides (Paper No. 03022004, at page 2, lines 13-19) or for physiologically functional equivalents such as conservative amino acid modifications and substitutions or nonconservative modifications or other undefined equivalents (Paper No. 03022004, at page 5, lines 1-6). Claims 1, 6, 9-19, 24, 27 and 28 have also been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement because, in the Examiner's assessment, the rejected claims "read on a method using literally any peptide with angiogenic activity that has fewer amino acids than thrombin, or less than 308 amino acids" (Paper No. 03022004, at page 7, lines 8-10) and the physiologically functional equivalents read on "molecules which differ from thrombin derivatives in particulars

which do not affect the function of the thrombin receptor binding domain or the serine esterase conserved amino acid sequence" (Paper No. 03022004, at page 8, lines 3-5).

Applicant respectfully disagrees with the Examiner's conclusion that the specification does not enable angiogenic thrombin derivative peptides or the physiologically functional equivalents as set forth in Claims 1, 6, 9-19, 24, 27 and 28. Applicant also disagrees with the Examiner's conclusion that Claims 1, 6, 9-19, 24, 27 and 28 contain subject matter which was not described in the specification in such a way as to reasonably convey that Applicant was in possession of the claimed genus of angiogenic thrombin derivative peptides and physiologically functional equivalents at the time the subject application was filed.

However, in an effort to advance prosecution in the subject application and without acquiescing to the Examiner's rejection or waiving the right to prosecute the full scope of the original claims in the future, Claims 1, 6, 9-19, 24, 27 and 28 have been cancelled. New Claims 23-41 recite the angiogenic thrombin derivative peptide Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID NO: 4).

Reconsideration and withdrawal of the rejection of Claims 1, 6-16, 21 and 22 are respectfully requested.

Items 7 and 8: Rejection of Claims 1-10, 13-14 and 28 Under 35 U.S.C. § 103(a)

Claims 1-10, 13-14 and 28 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Malinda *et al.* (U.S. Patent No. 6,197,751 B1) in view of Unger *et al.* (U.S. Patent No. 5,244,460) and Carney *et al.* (U.S. Patent No. 5,352,664). In support of the rejection, the Examiner alleges that it would have been obvious to one of ordinary skill in the art "to use the peptides of Carney et al. ('644) as angiogenic agents in the method of Malinda et al. with the expectation of beneficial results" (Paper No. 03022004, at page 9, last paragraph). The Examiner urges that "[m]otivation is provided by Unger et al. who disclose other angiogenic agents other than thymosin α1", which would have led one of ordinary skill "to expect that any angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al." (Paper No. 03022004, paragraph bridging pages 9 and 10). Applicant respectfully disagrees that the claims are obvious in view of the cited references.

Unger *et al.* would not have led one of ordinary skill in the art "to expect that *any* angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al.".

First, in the Background section, at Column 3, lines 31-36, Unger *et al.* state that:

> There is ***no*** technology in existence at the present time that can foster the in vivo growth of new blood vessels in the heart, thereby improving cardiac blood flow. That is why the somewhat unsatisfactory procedures described above are still necessary to improve cardiac blood flow.

Unger *et al.* note that one of these "unsatisfactory procedures" is a "one-time treatment" with FGF immediately following a myocardial infarction (injections are given during one 24 hour period of time) (Col. 2, ll. 45-48).

At Column 3, lines 37-35, Unger *et al.* express additional skepticism, stating that:

> During the last six years, a number of proteins have been characterized that promote the growth of blood vessels in vitro. Despite their great promise in the treatment of cardiovascular disease, ***none*** have been successfully utilized in vivo to date. Moreover, to the present date, there has been ***no*** publication of any data directed to using any of these proteins in vivo to generate any blood vessels in mature tissue, i.e., in non-embryonic tissue.

Further skepticism is highlighted at Column 3, lines 47-57, where Unger *et al.* state that:

> As stated above, polypeptides, to date, have not been successively used to promote the growth of blood vessels in the heart, to regenerate vessels in a damaged or nearby area in a heart, or over a period of time to increase cardiac blood flow in a damaged area. The focus of the prior art has been upon the prevention of damage immediately following arterial blockage in the heart or brain. Moreover, there is no method in the prior art to provide these results or any directional details or discussion relating to a suitable dosage for accomplishing regeneration of new cardiac blood vessels.

Unger *et al.* then state in the Summary of the Invention section, at Column 4, lines 6-12, that:

> It is an object of the present invention to provide a procedure or method by which peptides may be made operable in vivo to promote new cardiac blood vessel growth in mature cardiac tissue, when such peptides have been characterized or shown to promote the growth of blood vessels in vitro or in embryonic tissue.

At Column 4, lines 18-34, Unger *et al.* teach that such a method "to facilitate in a damaged heart or a heart in need of improved circulation the growth of cardiac blood vessels while reducing the risk of undesired vascularization in other areas of the body" comprises directly injecting a growth promoting peptide into the heart via a catheter and "repeating periodically on subsequent days" injection of the growth factor via the catheter. At Column 5, lines 1-7, Unger *et al.* define the phrase "repeating periodically on subsequent days" to mean:

> as continuing the step of injecting the peptide into the heart at more than one time on the same day, if necessary, and on additional designated days. The is significantly more than, and substantially different than just a one-day, single- or multiple-shot treatment in or around the time of a heart attack, which one-day injections are then not repeated.

In Examples 1 and 2, Unger *et al.* exemplify their method employing daily injections of two growth factors, VEGF and FGF (or fragments thereof), directly into the heart via a catheter.

Second, Malinda *et al.* is directed primarily towards wound healing using thymosin α1 (Tα1) peptide. Treatment of cardiac tissue damage using the Tα1 peptide is one of many treatments described by Malinda *et al.* In this particular treatment, it is said that the Tα1 peptide can induce angiogenesis in a tissue and stimulate collateral circulation in cardiac tissue affected by coronary occlusion, thereby restoring blood flow to ischemic tissues. See Col. 16, ll. 28-36. However, Malinda *et al.* do not provide any data to show that the Tα1 peptide has been used successfully to promote the growth of blood vessels in the heart, to regenerate vessels in a damaged or nearby area in a heart, or over a period of time to increase cardiac blood flow in a damaged area.

Thus, given the skepticism highlighted by Unger *et al.* and the absence of data in the prior art, one of ordinary skill in the art would not have been led to reasonably expect that any angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda *et al.*

Moreover, none of the cited references, either alone or in combination, teaches or suggests, with a reasonable expectation of success, that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence can be used to promote cardiac tissue repair, stimulate revascularization of cardiac tissue or inhibit vascular occlusion.

Malinda *et al.* teach that the Tα1 peptide is a 28 amino acid peptide which results from cleavage of the N-terminal region of pro-thymosin α1 (Col. 8, ll. 50-52). The amino acid sequence for this 28 amino acid peptide is reported to be SDAAVDTSSEITTKDLKEKKEVVEEAE N (see Malinda *et al.*, *J. Immunology*, 160:1001-1006 (1998); copy attached hereto as the Exhibit). The Tα1 peptide is not known to be a thrombin derivative peptide. Importantly, it is evident from the amino acid sequence for the Tα1 peptide that the Tα1 peptide does not comprise a thrombin binding domain or a serine esterase conserved sequence and therefore, the Tα1 peptide is unrelated to the angiogenic thrombin derivative peptides recited in Applicant's claims. Since the Tα1 peptide is not based on a thrombin sequence, one of ordinary skill in the art would not have been able to predict which thrombin fragments would have angiogenic activity, based on the teachings of Malinda *et al.*

As discussed above, Unger *et al.* teach a method in which a *growth promoting peptide* is directly injected via a catheter into a damaged heart or a heart in need of improved circulation to facilitate in the heart the growth of cardiac blood vessels (Col. 4, ll. 18-34). Unger *et al.* teach that growth promoting peptides that can be administered are epidermal growth factor, acidic fibroblast growth factor, basic fibroblast growth factor and vascular endothelial cell growth factor (Col. 5, ll. 45-49), as well as peptides "shown to have similar tissue growth stimulating functionality, either in vitro or in embryonic tissue" (Col. 5, ll. 49-53). Importantly, Unger *et al.* do not teach or suggest any peptides "shown to have similar tissue growth stimulating functionality, either in vitro or in embryonic tissue" other than the specific growth promoting peptides listed above. None of the specific growth promoting peptides disclosed by Unger *et al.* are considered to be thrombin derivative peptides. None of the specific growth promoting peptides disclosed by Unger *et al.* comprise a thrombin binding domain and serine esterase conserved sequence. Since the specific growth promoting peptides disclosed by Unger *et al.* are not based on a thrombin sequence, one of ordinary skill in the art would not have been able to predict which thrombin fragments would have angiogenic activity, based on the teachings of Unger *et al.* As such, Unger *et al.* do not cure the deficiencies of the Malinda *et al.* patent.

Carney *et al.* teach thrombin derivative peptides. Carney *et al.* do not teach or suggest the use of the thrombin peptide derivatives for promoting cardiac tissue repair, for stimulating revascularization of cardiac tissue, for stimulating vascular endothelial cell proliferation, for

inhibiting vascular occlusion or for inhibiting restenosis. As such, Carney *et al.* do not teach or suggest the use of the thrombin derivative peptides in the methods of Claims 1-7, 10-11 and 22. Accordingly, Carney *et al.* do not cure the deficiencies of the Malinda *et al.* and Unger *et al.* patents.

Accordingly, none of the cited references, alone or in combination, would have suggested the claimed methods (i.e., the methods of Claims 1-14 and 28 (now canceled) and the methods of new Claims 29-34 and 41) to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success. More specifically, none of the cited references, either alone or in combination, would have suggested that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence could be used to successfully promote cardiac tissue repair, stimulate revascularization of cardiac tissue, stimulate vascular endothelial cell proliferation or inhibit vascular occlusion. In fact, prior to Applicant's results described in the subject application (see Examples 3 and 4), one of ordinary skill in the art would not have reasonably expected that angiogenic thrombin derivative peptide comprising a thrombin binding domain and serine esterase conserved sequence can successfully promote formation of new blood vessels to help restore cardiac function to damaged or ischemic heart tissue.

Reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a) are respectfully requested.

Item 9: Rejection of Claims 11 and 12 Under 35 U.S.C. § 103(a)

Claims 11 and 12 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Malinda *et al.* (U.S. Patent No. 6,197,751 B1) in view of Unger *et al.* (U.S. Patent No. 5,244,460) and Carney *et al.* (U.S. Patent No. 5,352,664) and further in view of Thim *et al.* (U.S. Patent No. 5,912,229). Malinda *et al.*, Unger *et al.* and Carney *et al.* are applied as discussed above. In support of the rejection, the Examiner alleges that it would have been obvious to one of ordinary skill in the art "to place the peptides of Carney et al. ('644) into sustained release microcapsules [of Thim et al.] for administration according to the method of Malinda et al. with the expectation of attaining the well-known benefits of sustained release of medicine" (Paper No.

03022004, at page 10, lines 12-15). Applicant respectfully disagrees that the claims are obvious in view of the cited references.

Applicant notes that original Claims 11 and 12 ultimately depend from Claim 1. For the reasons set forth above, Unger *et al.* would not have led one of ordinary skill in the art "to expect that *any* angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al.". Additionally, Malinda *et al.*, Unger *et al.* and Carney *et al.*, either alone or in combination, do not teach or suggest that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and serine esterase conserved sequence can be used to promote cardiac tissue repair with a reasonable expectation of success.

Thim *et al.* teach the use of appetite-suppressing peptides, particularly the GLP-2 peptide, for treatment of obesity and type II diabetes. Thim *et al.* teach that the appetite-suppressing peptides, such as the GLP-2 peptide, may be formulated as sustained release formulations, particularly as microcapsules or microparticles, wherein the appetite-suppressing peptides are encapsulated by or dispersed in a biodegradable polymer such as polylactic acid, polyglycolic acid or a lactic acid/glycolic acid copolymer (Col. 10, ll. 10-17). However, Thim *et al.* do not provide any data to show that appetite-suppressing peptides, such as GLP-2 have been used successfully to promote the growth of blood vessels in the heart, to regenerate vessels in a damaged or nearby area in a heart, or over a period of time to increase cardiac blood flow in a damaged area. Thus, given the skepticism highlighted by Unger *et al.* and the absence of data in the prior art, one of ordinary skill in the art would not have been led to reasonably expect that any angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda *et al.*

Moreover, Thim *et al.* teach that the appetite-suppressing peptides have the following amino acid sequence: $X^1HX^2DGSFSDEMNTX^3LDX^4LAX^5X^6DFINWLX^7X^8TKITDX^9$, wherein X^1 is NH_2, DFPEEVAIVEELGRR, DFPEEVTIVEELGRR, DFPEEVNIVEELRRR, or a fragment thereof; X^2 is Ala or Gly; X^3 is Ile or Val; X^4 is Asn, Ser or His; X^5 is Ala or Thr; X^6 is Arg or Lys; X^7 is Ile or Leu; X^8 is Gln or His; or X^9 is OH, Lys, Arg, Arg-Lys, Lys-Arg, Arg-Arg or Lys-Lys (Col. 3, ll. 4-24). These appetite-suppressing peptides are not known to be thrombin derivative peptides. Importantly, it is evident from the amino acid sequence for the appetite-suppressing peptides that these peptides do not comprise a thrombin binding domain and a serine

esterase conserved sequence and therefore, the appetite-suppressing peptides are unrelated to the angiogenic thrombin derivative peptides recited in Applicant's claims. Since the appetite-suppressing peptides are not based on a thrombin sequence, one of ordinary skill in the art would not have been able to predict that the thrombin derivative peptide of SEQ ID NO: 4 would have angiogenic activity, based on the teachings of Thim *et al.* As such, Thim *et al.* do not teach or suggest the use of the thrombin derivative peptides in the claimed methods. Accordingly, Thim *et al.* do not cure the deficiencies of the Malinda *et al.*, Unger *et al.* and Carney *et al.* patents.

Accordingly, none of the cited references, alone or in combination, would have suggested the claimed methods (i.e., the methods of Claims 1-14 and 28 (now canceled) and the methods of new Claims 29-34 and 41) to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success. In particular, none of the cited references, either alone or in combination, would have suggested that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence could be used to successfully promote cardiac tissue repair.

Reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a) are respectfully requested.

Item 10: Rejection of Claims 15-17 and 20-27 Under 35 U.S.C. § 103(a)

Claims 15-17 and 20-27 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Malinda *et al.* (U.S. Patent No. 6,197,751 B1) in view of Unger *et al.* (U.S. Patent No. 5,244,460) and Carney *et al.* (U.S. Patent No. 5,352,664) and further in view of Saadat *et al.* (U.S. Patent No. 6,363,938 B2). Malinda *et al.*, Unger *et al.* and Carney *et al.* are applied as discussed above. In support of the rejection, the Examiner alleges that it would have been obvious to one of ordinary skill in the art "to coat stents with the peptides of Carney et al. ('644) as the bioactive agent when practicing the method of Saadat et al. with the expectation of achieving the beneficial results taught by Carney et al. ('644)" (Paper No. 03022004, at page 11, lines 5-8). The Examiner also alleges that since Saadat *et al.* "discuss stenosis ... and the action of the angiogenic agent", one of ordinary skill in the art "would immediately realize that, since the reason for use of the stent in the first place is to relieve stenosis then use of the angiogenic agent would by definition inhibit restenosis in the patient" (Paper No. 03022004, at page 11, lines

8-13). Applicant respectfully disagrees that the claims are obvious in view of the cited references.

Malinda *et al.*, Unger *et al.* and Carney *et al.* are discussed in detail above. Importantly, as discussed above, Unger *et al.* would not have led one of ordinary skill in the art "to expect that *any* angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al.". Additionally, Malinda *et al.*, Unger *et al.* and Carney *et al.*, either alone or in combination, do not teach or suggest that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence can be used to inhibit restenosis with a reasonable expectation of success. In fact, Malinda *et al.* teach that the Tα1 peptide disclosed therein can induce angiogenesis and stimulate collateral circulation in cardiac tissue affected by coronary occlusion, thereby restoring blood flow to ischemic tissues. Unger *et al.* teach that growth promoting peptides disclosed therein can induce the growth of cardiac blood vessels to facilitate the growth of cardiac blood vessels in the heart. Inducing angiogenesis and stimulating growth of new blood vessels have nothing to do with inhibiting restenosis.

Moreover, contrary to the Examiner's contention, Saadat *et al.* do not teach or suggest the use of stents to relieve stenosis. Rather, Saadat *et al.* teach the use of stents for forming channels in the epicardium at a position ***adjacent*** to a stenosed cardiac artery (Col. 11, ll. 29-35). Bioreactive agents included on stents inserted in the epicardium are said to encourage revascularization, including the growth of new networks of capillaries that provide blood to the tissue downstream of stenosis (Col. 11, ll. 38-41). More generally, Saadat *et al.* teach stents that are used for forming channels in a wall of a vessel or organ and that may include a bioactive agent that stimulates revascularization and/or tissue growth (Col. 4, ll. 61-65). The bioactive agent is said to stimulate tissue regeneration and/or vascularization in tissue ***adjacent*** to the stent following implantation (Col. 3, ll 41-44). Accordingly, contrary to the Examiner's assertion, one of ordinary skill in the art would not have reasonably been led to expect that the bioactive agents of Saadat *et al.* "would by definition inhibit restenosis in the patient." As such, Saadat *et al.* do not cure the deficiencies of the Malinda *et al.*, Unger *et al.* and Carney *et al.* patents.

Accordingly, none of the cited references, alone or in combination, would have suggested the claimed methods (i.e., the methods of Claims 15-26 (now cancelled) and the methods of new

Claims 35-39) to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success. None of the cited references, alone or in combination, would have suggested the claimed stent (i.e, the stent of Claim 27 (now cancelled) the stent of new Claim 40) to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success. In particular, none of the cited references, either alone or in combination, would have suggested that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence could be used to successfully inhibit restenosis. In fact, prior to Applicant's results described in the subject application (see Example 4), one of ordinary skill in the art would not have reasonably expected that angiogenic thrombin derivative peptide comprising a thrombin binding domain and serine esterase conserved sequence can successfully inhibit restenosis.

Reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a) are respectfully requested.

Item 11: Rejection of Claims 18 and 19 Under 35 U.S.C. § 103(a)

Claims 18 and 19 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Malinda *et al.* (U.S. Patent No. 6,197,751 B1) in view of Unger *et al.* (U.S. Patent No. 5,244,460), Carney *et al.* (U.S. Patent No. 5,352,664) and Saadat *et al.* (U.S. Patent No. 6,363,938 B2) and further in view of Nakahara *et al.* (U.S. Patent No. 6,191,113 B1). Malinda *et al.*, Unger *et al.*, Carney *et al.* and Saadat *et al* are applied as discussed above. In support of the rejection, the Examiner alleges that it would have been obvious to one of ordinary skill in the art "to coat the peptides of Carney et al. ('644) onto a balloon for administration with the expectation of achieving the benefits taught by Nakahara et al." (Paper No. 03022004, at page 12, lines 3-5). Applicant respectfully disagrees that the claims are obvious in view of the cited references.

Applicant notes that Claims 18 and 19 ultimately depend from Claim 15. For the reasons set forth above, Unger *et al.* would not have led one of ordinary skill in the art "to expect that *any* angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al.". Additionally, Malinda *et al.*, Unger *et al.*, Carney *et al.* and Saadat *et al.*, either alone or in combination, do not teach or suggest that an angiogenic thrombin

derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence can be used to inhibit restenosis with a reasonable expectation of success.

Nakahara *et al.* teach specific peptides for use in inhibiting growth of smooth muscle cells, and in preventing or treating arteriosclerosis associated with growth of smooth muscle cells, restenosis after PTCA or other angioplasties, luminal stenosis after grafting blood vessels and smooth muscle sarcoma (Col. 3, ll. 53-62). Nakahara *et al.* teach that the TFPI peptide is administered directly into the lesion of a blood vessel via a drug delivery catheter, coated on the surface of a stent or balloon which is then administered to the lesion of the blood vessel or introduced into the vein or artery as a bolus or continuously (Col. 6, ll. 24-31). Nakahara *et al.* teach that their peptides comprise a peptide (A) of an amino acid sequence abundant in basic amino acid residues and a peptide (B) of an amino acid sequence comprising at least two consecutive, hydrophobic amino acid residues wherein the peptide (B) is linked to the C-terminal of the peptide (A) (Col. 4, ll. 22-28). Nakahara *et al.* disclose specific examples of their peptides, including tissue factor pathway inhibitor (TFPI) peptides, at Column 4, line 29 to column 5, line 17. The peptides disclosed by Nakahara *et al.* are not thrombin derivative peptides. Importantly, it is evident from the amino acid sequences disclosed by Nakahara *et al.* for their peptides that they do not comprise a thrombin binding domain and a serine esterase conserved sequence and therefore, are unrelated to the angiogenic thrombin derivative peptides recited in Applicant's claims. Since the peptides disclosed by Nakahrar *et al.* are not based on a thrombin sequence, one of ordinary skill in the art would not have been able to predict that the thrombin derivative peptide of SEQ ID NO: 4 would be effective in inhibiting restenosis, based on the teachings of Nakahara *et al.* As such, Nakahara *et al.* do not teach or suggest that the angiogenic thombin derivative peptides recited in the claims can be used to successfully inhibit restenosis. As such, Nakahara *et al.* do not cure the deficiencies of the Malinda *et al.*, Unger *et al.*, Carney *et al.* and Saadat *et al.* patents.

Accordingly, none of the cited references, alone or in combination, would have suggested the claimed methods (i.e., the methods of Claims 15-26 (now cancelled) and the methods of new Claims 35-39) to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success. In particular, none of the cited references, either alone or in combination, would have suggested that an angiogenic thrombin derivative peptide comprising a thrombin

binding domain and a serine esterase conserved sequence could be used to successfully inhibit restenosis.

Reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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